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ORIGINAL PAPER

Factors that impact the outcomes in testicular germ cell tumors in low–middle-income countries

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Abstract

Germ cell tumors (GCTs) are one of the most common tumors in adolescents and young adults. There is paucity of data on GCT from low–middle-income countries (LMIC). The present study was conducted to assess the demographic features, clinical manifestations, pathology, and outcomes of GCT patients treated at our center. Patients with testicular GCT above the age of 18 years, treated at our center from 2001 to 2015 were included in the study. Data were extracted retrospectively from the case records. Event-free survival (EFS) and overall survival (OS) were calculated using the Kaplan–Meier method and the variables were compared using the log-rank test. The study included 421 patients among whom 128 (30%) had a histological diagnosis of seminoma and 293 (70%) had non-seminomatous germ cell tumor (NSGCT). Metastatic disease at presentation was observed in 83/128 (65%) with seminoma and 254/293 (87%) with NSGCT. According to the International Germ Cell Cancer Collaborative Group (IGCCCG) risk stratification for metastatic disease, good- and intermediate-risk seminoma were observed in 55/83 (66%) and 28/83 (34%) patients, respectively, and good-, intermediate-, and poor-risk NSGCT were observed in 82/254 (32%), 76/254 (30%), and 96/254 (38%) patients, respectively. The median follow-up was 32.3 months (range 0.03–200 months). The 3-year OS for the entire cohort was 80.3%. The 3-year OS for seminoma was 91.4%, and for NSGCT was 75.3%. Factors significantly associated with inferior EFS and OS on multivariate analysis included poor performance status, scrotal orchidectomy, carboplatin-based regimen, NSGCT histology, and treatment default. Patients with testicular GCT in India present in an advanced stage and higher IGCCCG risk compared to Western data. Factors unique to LMIC like treatment default, bulky disease, dose compromise, and scrotal orchidectomy have a negative impact on the outcome.

Keywords Testicular cancer · Germ cell tumor · Seminoma · NSGCT · IGCCCG risk

Introduction

Germ cell tumors (GCT) are one of the most common tumors in adolescents and young adult males [1]. GCTs commonly arise from the testis; and from retroperitoneum, mediastinum, and pineal and suprasellar locations [2]. GCTs are highly sensitive to chemotherapy and have an excellent prognosis [3]. Since it affects younger patients, implications on productivity and financial burden are an important issue. Unlike the developed countries, patients with GCT in low- and middle-income countries (LMIC) like India tend to present in an advanced stage with heavy nodal disease burden and treatment abandonments are more frequent. Cryptorchidism, a known risk factor for GCT is an important reason for delayed diagnosis in LMIC due to the associated social stigma. There is a paucity of data on testicular GCT from India and therefore, the present study was conducted to assess the demographic features, clinical manifestations, pathology, and outcomes of testicular GCT patients treated at our center.

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Patients and methods

Male patients with extra-cranial GCT above the age of 18 years, treated at our center from the year 2001 to 2015 were included in the study. Data were extracted retrospectively from the case records. The study is retrospective in nature and therefore ethics committee approval and patient consent are not required as per Cancer Institute ethics committee policy. Patients were diagnosed based on clinical findings, serum tumor markers including alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (HCG), imaging, and histological diagnosis. Patients with metastatic disease (stage II and III) were risk-stratified according to the International Germ Cell Cancer Group (IGCCCG) classification (Table 1) [4]. Patients with histological features of seminoma and normal serum AFP and HCG (elevated up to 200 IU/mL) were treated as seminoma and patients with elevated serum AFP or HCG and/or histological features of either yolk sac tumor, choriocarcinoma, embryonal carcinoma or malignant teratoma, and mixed features were treated as non-seminomatous germ cell tumor (NSGCT). Serum tumor markers were monitored prior to each cycle of chemotherapy. Treatment decisions for individual patients were taken by the multidisciplinary tumor board. Patients in whom orchidectomy could not be performed at presentation due to reasons like poor performance status or significant comorbidities, it was performed either after 2 cycles of chemotherapy or at the end of the planned chemotherapy. The IGCCCG risk stratification in patients who underwent interval orchidectomy was based on the baseline pre-operative tumor markers and in patients who underwent orchidectomy at diagnosis, it was based on post-operative markers prior to initiation of chemotherapy [4].

Computed tomographic (CT) scan of the chest, abdomen, and pelvis was performed at presentation for staging the disease and was repeated after completion of planned chemotherapy. Ultrasound of testis was also performed at presentation. Bleomycin, etoposide, and cisplatin (BEP) or etoposide and cisplatin (EP) was the most commonly used chemotherapeutic regimen [5–10]. Carboplatin was used if cisplatin was contraindicated. Usually, at least 4 cycles of BEP/EP were administered prior to re-evaluation in metastatic disease. In non-metastatic NSGCT with adverse prognostic features, patients received 2 cycles of BEP or EP [11]. In non-metastatic seminoma, it was either para-aortic radiation for 20 cGY or one cycle of carboplatin [12]. Responses were captured as recorded in the case records. The decision to perform retroperitoneal lymph node dissection (RPLND) and/or metastasectomy for the post-chemotherapy residual disease was individualized and was taken after discussion in the multi-specialty board. According to our institution policy, RPLND is performed in patients with NSGCT with a post-chemotherapy retroperitoneal nodal mass more than 1 cm and normal tumor markers and in seminoma with a retroperitoneal nodal mass more than 3 cm that is positive on a positron emission tomography (PET) combined with CT. Prior to the availability of PET/CT at our institution, patients with seminoma who had a post-chemotherapy retroperitoneal nodal mass more than 6 cm on CT scan were treated with radiation and those with less than 6 cm mass were observed.

After completion of the planned treatment, patients were followed up monthly for the first year, every 3 months for 2nd and 3rd year, every 6 months for 4th and 5th year, and

Table 1 Prognostic-based staging system for metastatic germ cell cancer (International Germ Cell Cancer Collaborative Group) [4]

Good-prognosis group	
NSGCT (56% of cases) 5-year PFS 89% 5-year OS 92%	All of the following criteria Testis/retroperitoneal primary No non-pulmonary visceral metastases AFP < 1000 ng/mL hCG < 5000 IU/L (1,000 ng/mL) LDH < 1.5 × ULN Seminoma
Seminoma (90% of cases) 5-year PFS 82% 5-year OS 86%	All of the following criteria No non-pulmonary visceral metastases Normal AFP Any hCG Any LDH
Intermediate prognosis group	
NSGCT (28% of cases) 5-year PFS 75% 5-year OS 80%	All of the following criteria Testis/retroperitoneal primary No non-pulmonary visceral metastases AFP > 1,000 and < 10,000 ng/mL or hCG > 5,000 and < 50,000 IU/L or LDH > 1.5 and < 10 × ULN
Seminoma (10% of cases) 5-year PFS 67% 5-year OS 72%	Any of the following criteria Any primary site Non-pulmonary visceral metastases Normal AFP Any hCG Any LDH
Poor prognosis group	
NSGCT (16% of cases) 5-year PFS 41% 5-year OS 48%	Any of the following criteria Mediastinal primary Non-pulmonary visceral metastases AFP > 10,000 ng/mL or hCG > 50,000 IU/L (10,000 ng/mL) LDH > 10 × ULN
Seminoma	No patients classified as poor prognosis

NSGCT Non-seminomatous germ cell tumor, *PFS* progression-free survival, *OS* overall survival, *AFP* alpha-fetoprotein, *hCG* human chorionic gonadotrophin, *ULN* upper limit of normal, *LDH* lactate dehydrogenase

thereafter yearly. Patients underwent clinical examination and testing of serum AFP and HCG during follow-up. CT chest, abdomen, and pelvis or chest X-ray with ultrasound abdomen and pelvis were performed at 6 months and 1 year of follow-up. The choice of follow-up imaging was based on physician discretion. Ultrasound of the abdomen and pelvis and Chest X-ray were usually performed every 6 months after the first year of follow-up for a total of 3–4 years.

Event in the study was defined as disease relapse/progression or death due to any cause. Event-free survival (EFS) was calculated from the date of initiation of treatment to the date of the event and overall survival (OS) was calculated from the date of initiation of treatment to the date of last follow-up or date of death. For survival analysis, all patients were censored at the date of last follow-up or date of telephonic/postal contact if lost to follow-up or December 01, 2017, whichever was earlier. EFS and OS were analyzed by the Kaplan–Meier method and risk factors were compared using the log-rank test for univariate analysis and Cox-proportional hazards model for multivariate analysis. SPSS version 17.0 (SPSS Inc, IBM, Chicago) was used for statistical analysis.

Results

The study included 421 patients with extra-cranial GCT treated at our center between 2001 and 2015. Seminoma was diagnosed in 128 (30%) patients and NSGCT in 293 (70%) patients. The median age for all the patients was 32 years (range 18–74 years), for seminoma 35 years (range 19–70 years), and NSGCT 29 years (range 18–74 years). Classical seminoma (92%) and mixed GCT (more than one subtype of GCT) (56%) were the most common pathological subtype observed in seminoma and NSGCT, respectively. Eighty-four patients presented in stage I (20%), 91 in stage II (22%), and 246 presented in stage III (58%).

The primary site of disease was testis in 408 patients (97%), retroperitoneum in 8 (2%), and Mediastinum in 5 (1%). Incidence of undescended Testis was 10% ($n=41$) among whom 23 developed seminoma (56%) and 18 NSGCT (44%).

Orchidectomy was performed in 383/421 (91%) patients. Thirty-eight patients did not undergo orchidectomy; 2 of which had a retroperitoneal primary, 5 had a mediastinal primary, 12 had undescended testis, and 19 with testicular primary defaulted or died before orchidectomy could be performed. Among the 383 patients who underwent orchidectomy, high inguinal orchidectomy was performed in 263 patients, scrotal orchidectomy in 94, excision of cryptorchid testicular mass in 20, hemi-scrotectomy in 3, and details of the type of orchidectomy were not available for 3 patients. All patients who underwent scrotal orchidectomy had their surgery done prior to presentation to our hospital. Orchidectomy prior to starting chemotherapy was performed in 330 patients, while 53 patients underwent interval orchidectomy after receiving chemotherapy. Baseline demographic data and treatment details have been provided in Table 2.

Eighty-four patients (45 seminomas and 39 NSGCT) had non-metastatic disease and 337 (83 seminomas and 254 NSGCT) had metastatic disease.

Non-metastatic seminoma

Forty-five patients were diagnosed to have stage I seminoma, among whom 28 were treated with radiotherapy, 1 underwent RPLND, 5 patients were kept under observation, and 11 received chemotherapy (2 patients EP, 3 BEP, and 6 Carboplatin). None of the patients had an event.

Metastatic seminoma

Among 83 patients with Stage II and Stage III Seminoma, 55 were IGCCCG Good risk (66%) and 28 were Intermediate risk (34%). Seventy-six patients received chemotherapy (45 EP, 29 BEP, 2 Carboplatin). Seven patients with metastatic seminoma did not receive chemotherapy and this included 6 patients who were treated with radiotherapy and 1 patient who defaulted without starting treatment. Treatment response could be assessed in 69/83 patients among whom 62/69 (90%) had a complete response (CR), 6/69 (8%) had a partial response (PR), and 1/69 (2%) had progressive disease (PD). Response assessment data were not available for 14 patients the reasons being treatment abandonment in 13 patients and death in one.

Non-metastatic NSGCT

Thirty-nine patients had stage I NSGCT, among whom 1 underwent RPLND, 6 were observed, and 32 received chemotherapy (3 EP, 29 BEP). None of the patients had an event.

Metastatic NSGCT

Among 254 NSGCT patients with Stage II and Stage III disease, 82 were IGCCCG good risk (32%), 76 were intermediate risk (30%), and 96 were poor risk (38%). Two-hundred forty-seven patients received chemotherapy (35 EP, 193 BEP, 5 Carboplatin, and 14 other drugs). Seven patients with metastatic NSGCT did not receive chemotherapy and this included 6 patients who defaulted prior to initiation of treatment and one patient who took treatment elsewhere. Two patients underwent high-dose chemotherapy (HDCT) with autologous hematopoietic stem cell transplant (ASCT) at relapse and both are alive and in CR at last follow-up. Response assessment details after planned

Table 2 Patient characteristics and treatment received

Characteristic	Number (%)
Location of primary tumor	
Testis	408 (96.9)
Retroperitoneum	8 (1.9)
Mediastinum	5 (1.2)
Undescended testis	41 (9.7)
Orchidectomy type	
Scrotal	97 (25.6)
HIO	283 (74.4)
Not done	41 (9.7)
Upfront	327 (86)
Interval	53 (14)
Tumor histology	
Seminoma	128 (30%)
NSGCT	293 (70%)
Predominant histology	
Embryonal carcinoma	30 (7.1)
Yolk sac tumor	11 (2.6)
Immature teratoma	11 (2.6)
Mature teratoma	13 (3.1)
Mixed GCT	162 (38.4)
Subtype not available	65 (15.4)
Classical seminoma	119 (28.3)
Anaplastic seminoma	8 (2)
Spermatocytic seminoma	2 (0.5)
Metastatic site(s)	
Retroperitoneum	281 (66.7)
Pulmonary	143 (34)
NPVM	30 (7.1)
Liver	27 (6.4)
Brain	6 (1.4)
Bone	4 (1)
Other (penile, oral)	2 (0.5)
IGCCCG risk stratification Seminoma	
Good	55 (66)
Intermediate	28 (44)
NSGCT	
Good	82 (32)
Intermediate	76 (30)
Poor	96 (38)
First-line chemotherapy	
BEP	253 (60)
EP	86 (20)
VIP	2 (2.4)
Carboplatin	13 (15.5)
Other	26 (31)

NPVM Non-pulmonary visceral metastasis, *IGCCCG* International Germ Cell Cancer Collaborative Group, *NSGCT* non-seminomatous germ cell tumor, *HIO* high inguinal orchidectomy

treatment were available for 197/254 patients, among whom 141/197 (72%) had CR, 20/197 (10%) had PR, 1/197 had stable disease (SD), and 35/197 (18%) had progressive disease (PD). Response assessment details were not available for 57 patients, among whom 9 had died prior to treatment completion, data were not available in 4 and 44 had abandoned treatment.

Toxicity

Bleomycin lung toxicity was observed in 4 patients, 1 patient had sepsis-related cardiac dysfunction, and 2 had sensorineural hearing loss. Incidence of grade 3 or 4 febrile neutropenia was 13.3% ($n=56$). Five patients died due to sepsis; 4 were secondary to febrile neutropenia and one patient had intestinal obstruction and non-neutropenic sepsis. Second malignancy occurred in 11 patients; sarcoma in 4, bladder cancer, renal cell carcinoma, prostate cancer, thyroid cancer, ependymoma, melanoma, and squamous cell carcinoma of the skin in 1 each. Only 1/11 patients with second malignancy had received prior radiotherapy.

Post-chemotherapy residual disease

RPLND was performed in 115 patients, among whom 13 had seminoma and 102 had NSGCT. Four out of 115 (3%) had marker elevation during RPLND. Viable tumor was detected in 29 (25%), mature teratoma in 26 (23%), and no viable tumor in 60 patients (52%). Pulmonary metastasectomy was performed in 11 patients and a viable tumor was detected in 1, mature teratoma in 5 (45%), and no viable tumor in 5 (45%). In patients who underwent both RPLND and pulmonary metastasectomy ($n=9$), concordance rate of pathology was 55%. The concordance rate of bilateral pulmonary metastasectomy was 66% ($n=3$). Liver metastasectomy was performed in 4 patients and 1 was positive for viable tumor (25%), 1 was showed mature teratoma (25%), and 2 were negative for viable tumor (50%). The concordance rate of histology for RPLND and liver metastasectomy was 100% ($n=3$). Retrograde ejaculation after RPLND occurred in 11 patients (9.6%).

Salvage chemotherapy

Fifty patients relapsed; out of which 41 (9 seminomas and 32 NSGCT) received salvage chemotherapy, the rest 9 patients either abandoned treatment or were not fit for treatment. Salvage regimen used were VeIP (Vinblastine, Ifosfamide, Cisplatin) in 16 patients (39%), VIP in 9 (22%), TIP (Paclitaxel, Ifosfamide, Cisplatin) in 4 (10%), IPO (Irinotecan, Paclitaxel, Oxaliplatin) in 4 (10%), EP in 4 (10%), VeIP/TIP in 2 (5%), IPO/TIP in 1 (2%), and ICE (Ifosfamide, Carboplatin, Etoposide) in 1 (2%). 12 patients achieved CR

after first salvage (30%), 4 achieved PR (10%), 18 had PD (44%), and 7 patients defaulted (17%). Eleven patients had a second relapse; they were treated with salvage TIP in 7 patients (64%), IPO in 2 patients (18%), POMB/ACE (Cisplatin, Vincristine, Methotrexate, Bleomycin / Actinomycin-D, Cyclophosphamide, Etoposide) in 1 patient (9%), and ICE in 1 patient (9%). After the second salvage chemotherapy, 2 patients achieved CR and 9 had PD.

Mortality

Seventy-six patients died during the period of study. Progressive disease was the most common cause of death in 62 patients (82%), febrile neutropenia in 4 (6%), bleomycin lung toxicity in 1 (2%), pulmonary embolism in 1 (2%), fulminant hepatitis in 2 (2%), intestinal obstruction in 2 (2%), ischemic heart disease in 2 (2%), and unknown cause in 2 (2%).

Survival analysis

Median follow-up was 32.3 months (range 0.1–200 months). The 3-year EFS and OS of the entire cohort were 73.5% and 80.3%, respectively. The 3-year EFS and OS of the seminoma group were 87.1% and 91.4%, respectively, and the NSGCT group were 67.4% and 75.3%, respectively. The 3-year EFS and OS of the IGCCCG good-risk seminoma patients were 80.5% and 89.4%, respectively, and Intermediate-risk seminoma were 78.3% and 80.9%, respectively ($P = 0.684$ for EFS and 0.409 for OS) (Fig. 1). The 3-year EFS and OS of the IGCCCG good-risk NSGCT patients were 76.1% and 83.4%, respectively, intermediate-risk NSGCT were 73.2% and 81.5%, respectively, and poor-risk NSGCT were 41% and 52.3%, respectively ($P < 0.001$) (Fig. 2). Patients with stage I NSGCT and seminoma had 100% EFS and OS. On univariate analysis of all patients, chemotherapy dose compromise, treatment default, scrotal orchidectomy, poor performance status, carboplatin use, retroperitoneal nodal mass more than 10 cm, and IGCCCG poor risk was associated with inferior EFS and OS (Table 3). On multivariate analysis of all patients, factors significantly associated with inferior EFS and OS were poor performance status ($P < 0.0001$ for EFS and OS), scrotal orchidectomy ($P = 0.043$ and 0.001), carboplatin-based regimen ($P < 0.0001$ for EFS and OS), NSGCT histology ($P = 0.001$ and 0.007), and treatment default ($P < 0.0001$ and 0.003).

Univariate analysis for factors prognostic for EFS and OS in seminoma and NSGCT has been provided in Tables 4 and 5, respectively. On multivariate analysis for factors predicting EFS in NSGCT, carboplatin-based chemotherapy ($P < 0.0001$), retroperitoneal node size > 10 cm ($P = 0.038$), and reduction in chemotherapy dose intensity ($P = 0.01$) predicted inferior EFS. On multivariate analysis for factors predicting OS in NSGCT, poor performance status ($P < 0.0001$), carboplatin-based chemotherapy ($P < 0.0001$), IGCCCG poor risk ($P = 0.039$), scrotal orchidectomy ($P = 0.012$), and treatment default ($P < 0.005$) predicted inferior outcome. Treatment default ($P = 0.018$) predicted poor EFS for patients with seminoma on multivariate analysis and none of the factors significantly predicted the OS.

Fifty-seven (14%) patients abandoned treatment while receiving chemotherapy or prior to RPLND and 57 (14%) patients were lost to follow-up after completion of treatment.

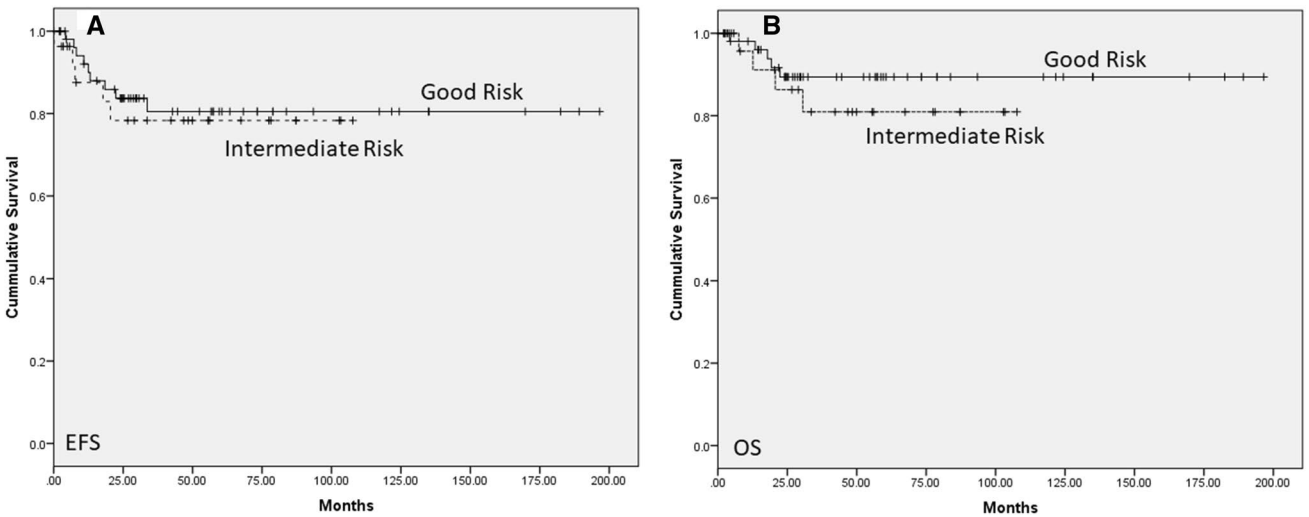

Fig. 1 Kaplan–Meier survival curves for **a** EFS and **b** OS for seminoma according to the IGCCCG risk stratification

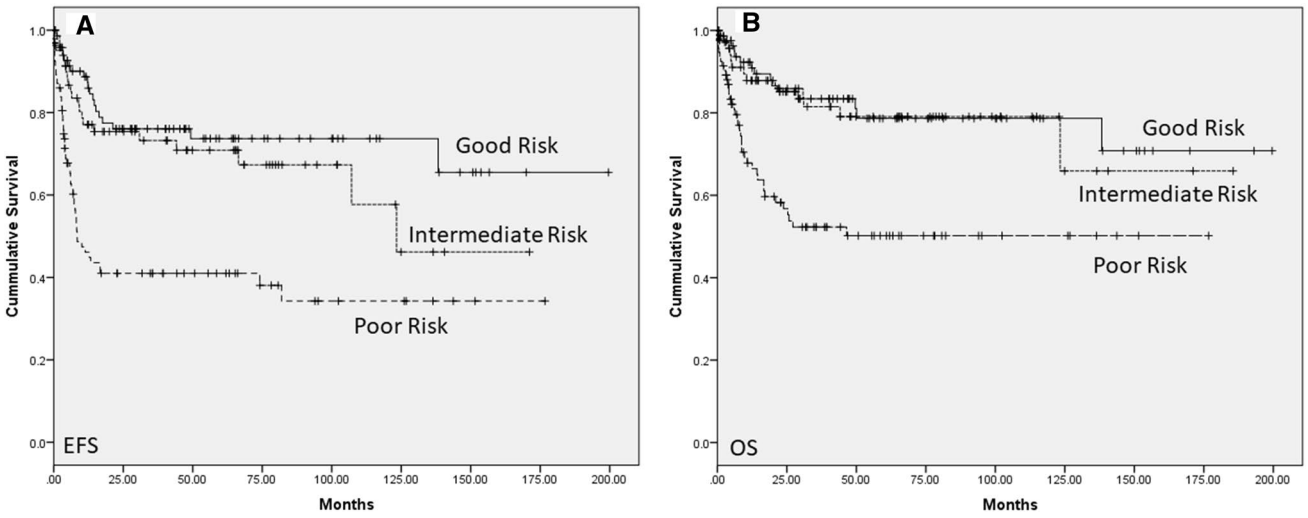

Fig. 2 Kaplan–Meier survival curves for **a** EFS and **b** OS for NSGCT according to the IGCCCG risk stratification

Discussion

GCT although common in adolescents and young adults is a rare cancer and is not among the top ten cancers seen in India [13]. Treatment of GCT was revolutionized by the discovery of the sensitivity to platinum chemotherapy and the high cure rate in GCT is considered as one of the successful achievements in oncology [3].

Enough data are available from the developed countries on the demographic features, management, and outcome of testicular GCT. However, the same is not true for LMIC like India [14–17]. Delayed presentation, advanced stage, treatment abandonment, and inappropriate treatments are challenges that physicians face in India when managing GCT and therefore extrapolating data from the West to manage our patients may not be informative.

In a large series published by from the Indiana University, USA, the proportion of patients who had IGCCCG good-risk, intermediate-risk, and poor-risk disease was 64%, 10%, and 26%, respectively [18]. In contrast in our study, the proportion of patients who had IGCCCG good-risk, intermediate-risk, and poor-risk disease was 41%, 31%, and 28%, respectively. Our data clearly show that the burden of advanced disease in the Indian subcontinent is more than what is seen in the West and therefore the outcomes would also be inferior (Table 6).

NSGCT was more common in our study and this has also been reported in the literature. However, mixed GCT (38.5%) was the commonest histology in our series and seminoma constituted 30% of all cases, whereas Albany et al. reported Embryonal carcinoma (36.5%) as the most common histology in their series and seminoma constituted 9% of cases [18]. The overall incidence of seminoma is increasing and NSGCT is reducing in the West [19]. Majority of adult GCT patients are the breadwinners of the family and those who belong to poor socio-economic strata of the society cannot take a prolonged absence from work for treatment. Therefore, there tends to be a higher rate of treatment abandonment and loss to follow-ups. In our study, 14% of the patients abandoned treatment and 14% of the patients were lost to follow-up after completing treatment.

OS was inferior in patients who underwent interval orchidectomy in comparison to patients who underwent orchidectomy at presentation (76.2% vs 83.4%), this was not statistically significant ($P=0.37$). Poor performance status, malnutrition, and bulky abdominal masses make many patients unsuitable for orchidectomy at presentation at our center and therefore these patients are started on chemotherapy and undergo surgery after an improvement in their general physical condition.

Scrotal orchidectomy was an important predictor of an inferior OS. All the patients who underwent scrotal orchidectomy had the procedure prior to presentation to our hospital. Lack of awareness among treating surgeons on the importance of high inguinal orchidectomy in testicular cancers and misdiagnosis as hydrocele or hematoma are important reasons for many patients undergoing scrotal orchidectomy. Patients who undergo scrotal orchidectomy are more likely to present late and with advanced disease due to delayed referral by the treating doctor. Scrotal orchidectomy disrupts the lymphatic drainage and there is 8.6% increased chance of local recurrence [20]. However, the role of hemiscrotectomy and prophylactic inguinal nodal dissection in patients who undergo scrotal orchidectomy is not proven [21]. Second malignancy was seen in 2.6% of patients in our study. A recent publication reported an incidence of 6% second malignancy in a cohort of 5848 patients with testicular cancer [22]. An increase in solid malignancies was seen

Table 3 Univariate analysis for EFS and OS for all patients

Parameter (*N*)	3-Year EFS (%)	*P* value	3-Year OS (%)	*P* value
Performance score				
PS 0–1 (388)	78.3	< 0.001	85.4	< 0.001
PS > 1 (33)	12.2		30.6	
Smoking				
Yes (129)	68.5	0.324	80.5	0.810
No (292)	75.6		80.2	
Alcohol intake				
Yes (110)	63.1	0.034	74.9	0.231
No (311)	76.8		81.9	
Undescended testis				
Yes (41)	79.1	0.186	79.6	0.841
No (380)	72.8		80.4	
Orchidectomy				
Upfront (327)	75.4	0.682	83.4	0.371
Interval (53)	74.6		76.2	
Orchidectomy				
HIO (283)	80.1	0.016	86.7	< 0.001
Scrotal (97)	63.1		71.9	
Histology (metastatic disease)				
Seminoma (83)	87.1	< 0.001	91.4	< 0.001
NSGCT (254)	67.4		75.3	
IGCCCG risk				
Good (137)	78	< 0.001	85.8	< 0.001
Intermediate (104)	74.5		81.3	
Poor (96)	41		52.3	
RP nodes[+]				
N1 (25)	87.1		91.3	
N2 (52)	84.4	< 0.001	88.8	< 0.001
N3 (204)	59.1		68.6	
RP nodal size				
< 10 cm (198)	73.1	< 0.001	80.3	0.009
> 10 cm (108)	55		64.9	
Chemotherapy				
Cisplatin based (335)	72.3	0.006	79.9	< 0.001
Carboplatin based (20)	52		53.1	
Dose compromise				
Yes (49)	48.2	< 0.001	55.2	< 0.001
No (307)	75		82.2	
Chemotherapy duration (4 cycles)				
< 12 weeks (131)	85.1	< 0.001	90.6	0.001
> 12 weeks (71)	61.1		74.5	
Defaulted treatment/LFU				
Yes (114)	42.2	< 0.001	58.7	< 0.001
No (307)	80.5		85	

N1: Metastasis with a lymph node mass 2 cm or less in greatest dimension or multiple lymph nodes, none more than 2 cm in greatest dimension

N2: Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, any one mass more than 2 cm but not more than 5 cm in greatest dimension

N3: Metastasis with a lymph node mass more than 5 cm in greatest dimension

HIO High inguinal orchidectomy, *RP* retroperitoneal, *EFS* event-free survival, *OS* overall survival, *RP* retroperitoneal, *IGCCCG* International Germ Cell Cancer Collaborative Group, *NSGCT* non-seminomatous germ cell tumor, *HIO* high inguinal orchidectomy, *LFU* lost to follow-up

[+]Retroperitoneal nodal size definition

Table 4 Univariate analysis for patients with seminoma

Parameter (*N*)	3-Year EFS (%)	*P* value	3-Year OS (%)	*P* value
Performance score				
PS 0–1 (125)	88.6	< 0.001	92.2	< 0.001
PS > 1 (3)	50		66.7	
Smoking				
Yes (46)	85.7	0.987	94.7	0.405
No (82)	87.5		89.7	
Alcohol intake				
Yes (30)	81.5	0.562	91.8	0.993
No (98)	88.4		91.4	
Undescended testis				
Yes (23)	94.1	0.288	94.1	0.603
No (105)	85.6		90.8	
Orchidectomy				
Upfront (109)	86.2	0.868	91.2	0.705
Interval (10)	90		90	
Orchidectomy				
HIO (95)	89	0.077	92.7	0.235
Scrotal (24)	76		83.3	
IGCCCG risk				
Good (55)	80.5	0.684	89.4	0.409
Intermediate (28)	78.3		80.9	
RP nodes^{+}				
N1 (8)	73		85.7	
N2 (18)	94	0.002	94	0.012
N3 (54)	75		83.2	
RP nodal size				
< 10 cm (50)	78.4	0.914	88.2	0.681
> 10 cm (30)	81.2		83	
Chemotherapy				
Cisplatin based (76)	81.1	0.006	86.9	0.895
Carboplatin based (11)	91		90	
Dose compromise				
Yes (8)	83.3	0.124	83.3	0.115
No (78)	83.2		88.7	
Chemotherapy duration (4 cycles)				
< 12 weeks (66)	86	0.633	90	0.780
> 12 weeks (62)	89		92.8	
Defaulted treatment/LFU				
Yes (29)	67.1	< 0.001	81.8	0.096
No (99)	92.5		93.2	

HIO High inguinal orchidectomy, *RP* retroperitoneal, *EFS* event-free survival, *OS* overall survival, *RP* retroperitoneal, *IGCCCG* International Germ Cell Cancer Collaborative Group, *HIO* high inguinal orchidectomy, *LFU* lost to follow-up

in their cohort and gastrointestinal malignancies were the most common in their study [22]. Platinum and etoposide are common agents implicated in second malignancies, but these are usually hematological in nature, whereas, all the second malignancies in our cohort were solid tumors.

Carboplatin has been shown to be inferior to cisplatin for treating NSGCT in adults unlike in children where they have been shown to be equivalent [23, 24]. The higher dose of carboplatin in the pediatric study (area under the curve [AUC] 7.9 mg/mL per minute) in comparison to the adult studies (AUC 5 mg/mL per minute) may be the reason for equivalence between carboplatin and cisplatin in children [25]. The Malignant Germ Cell International Consortium (MaGIC) trial is being planned to see if the pediatric strategy

Table 5 Univariate analysis for patients with NSGCT

Parameter (*N*)	3-Year EFS (%)	*P* value	3-Year OS (%)	*P* value
Performance score				
PS 0–1 (263)	73.4	< 0.001	82.1	< 0.001
PS > 1 (30)	13		16.2	
Smoking				
Yes (83)	58.2	0.126	72.2	0.333
No (210)	70.9		76.5	
Alcohol intake				
Yes (80)	55.6	0.072	68.4	0.291
No (213)	71.5		77.4	
Undescended testis				
Yes (18)	61.2	0.968	62.7	0.335
No (275)	67.7		76.2	
Orchidectomy				
Upfront (221)	70	0.939	79.5	0.371
Interval (43)	70.8		72.3	
Orchidectomy				
HIO (191)	75	0.096	82.5	0.012
Scrotal (73)	58		68.9	
IGCCCG risk				
Good (82)	76.1		85.8	
Intermediate (76)	73.2	< 0.001	81.3	< 0.001
Poor (96)	41		52.3	
RP nodes^{+}				
N1 (17)	93.8		93.8	
N2 (46)	80	< 0.001	86.9	< 0.001
N3 (163)	53.8		63.7	
RP nodal size				
<10 cm (148)	71.3	< 0.001	77.7	0.004
>10 cm (78)	44.1		57.6	
Chemotherapy				
Cisplatin based (259)	69.7	0.006	77.8	< 0.001
Carboplatin based (9)	10.5		11	
Dose compromise				
Yes (41)	41.9	< 0.001	50.6	0.001
No (229)	72		80	
Chemotherapy duration (4 cycles)				
<12 weeks (191)	73	0.013	79.1	0.135
>12 weeks (102)	56		67.3	
Defaulted treatment/LFU				
Yes (85)	37.3	< 0.001	51.3	< 0.001
No (208)	74.8		81	

HIO High inguinal orchidectomy, *RP* retroperitoneal, *EFS* event-free survival, *OS* overall survival, *RP* retroperitoneal, *IGCCCG* International Germ Cell Cancer Collaborative Group, *NSGCT* non-seminomatous germ cell tumor, *HIO* high inguinal orchidectomy, *LFU* lost to follow-up

of using a higher dose of carboplatin is effective in adolescents and young adults with NSGCT [26]. We use carboplatin in patients who are sick and moribund at presentation, malnourished, have renal dysfunction, hearing deficits, or cardiac issues that contradict the use of cisplatin.

HDCT followed by ASCT is a curative option for some patients with relapsed or refractory NSGCT [3]. Data from Indiana University have shown that ASCT can be curative in patients even after 2nd relapse or beyond [27]. In our cohort, only two patients received HDCT followed by ASCT. The

Table 6 Comparison of survival outcomes between Indiana University, IGCCCG, NCI, and present study

IGCCCG risk		Indiana University (1998–2014), 5 year [18]	IGCCCG (1975–1990), 5 year [4]	NCI SEER (2000–2013), 5 year [28]	Present Study (2001–2015), 3 year[a]
Good risk	PFS	90	88	NA	78
	OS	97	91		85.8
Intermediate risk	PFS	84	75	NA	74.5
	OS	92	79		81.3
Poor risk	PFS	54	41	NA	41
	OS	73	48		52.3
Testis cancer cohort	OS	94	NA	75	80.3

IGCCCG International Germ Cell Cancer Collaborative Group, *PFS* progression-free survival, *OS* overall survival, *NCI SEER* National Cancer Institute Surveillance, Epidemiology, and End Results Program, *NA* not available

[a]Event-free survival

cost of HDCT and ASCT is a major factor why this modality was not offered to most of our relapsed/refractory patients.

Patients in our cohort in whom the chemotherapy dose intensity was reduced or in whom the chemotherapy duration exceeded 12 weeks had inferior survival outcomes (Table 2). This reiterates the importance of maintaining chemotherapy dose intensity and schedule in a highly chemotherapy-sensitive tumor like GCT.

Patients presenting with large retroperitoneal lymph nodes are not unusual in our setting. In our study, patients with a retroperitoneal nodal size of more than 10 cm had an inferior OS compared to patients with a retroperitoneal nodal size of less than 10 cm.

Advanced disease at presentation, bulky retroperitoneal nodal mass, treatment abandonment, failure to maintain dose intensity, and scrotal orchidectomy are important factors that contribute to reduced survival in our GCT cohort when compared to western data. However, most patients in our cohort with IGCCCG good and intermediate-risk are long-term survivors and 50% of poor-risk patients have favorable outcomes.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Informed consent and ethical approval The study is retrospective in nature and therefore ethics committee approval and patient consent are not required as per Cancer Institute ethics committee policy.

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